REMARKS

Claims 45, 46, 49-54, 56-61, and 64-72 are pending in this application. Claims 45-46, 58-61, and 72 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld (U.S. Patent No. 4,016,252; hereinafter "Relyveld") in combination with Poser et al. (U.S. Patent No. 5,968,253; hereinafter "Poser"). Claims 49-54, 56-57, and 64-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Poser and Classen (U.S. Patent No. 5,723,283; hereinafter "Classen"). Finally, claims 45-46, 58-61, and 72 are rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Gerhart et al. (U.S. Patent No. 5,085,861; hereinafter "Gerhart"), and Constantz et al. (U.S. Patent No. 5,782,971; hereinafter "Constantz"). By this reply, Applicants address each of the Examiner's rejections.

Rejections under 35 U.S.C. § 103

Relyveld in Combination with Poser

Claims 45-46, 58-61, and 72 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Poser. In the present Office Action, the Examiner states:

> it would have been obvious to one of skill in the art at the time of invention to modify the physical characteristics of Relyveld's formulation according to the teachings of Poser and change the gel formulation of Relyveld's vaccine to a paste-like formulation by routine experimentations to optimize the described calcium phosphate concentrations. (Office Action, p. 4.)

Applicants respectfully traverse this rejection.

In the Reply to Final Office Action, filed on Feburary 15,2006, Applicants submitted a Combined Declaration under 37 C.F.R. § 1.131 and § 1.132, and argued that Poser had been removed as a prior art reference based on the fact that PCT/US97/18528 (Applicants' own

application; a copy of which is enclosed), which was filed on October 16, 1997 (i.e., prior to Poser), is evidence showing possession by the Applicants of at least as much of the invention of present claims 45-46, 58-61, and 72 as is shown by Poser.[1] The Declaration was provided to antedate Poser, which is prior art under 35 U.S.C. § 102(a), on the basis of *In re Stempel* (241 F.2d 755, 113 U.S.P.Q. 77 (C.C.P.A. 1957), which stands for the proposition that a reference can be removed by an affidavit under Rule 131 showing prior reduction to practice of as much of the claimed invention as the reference shows (i.e., the "Stempel rule"). Applicants did not submit the Declaration in an attempt to constructively claim the benefit of the filing date of the prior filed PCT application under 35 U.S.C. §§ 120, 121, or 365(c), as is suggested by the Examiner (see page 8 of the Office Action).

Applicants direct the Examiner to M.P.E.P. § 715.03(I)(B), which states:

> Where the only pertinent disclosure in the reference or activity is a single species of the claimed genus, the applicant can overcome the rejection directly under 37 CFR 1.131 by showing prior possession of the species disclosed in the reference or activity. On the other hand, a reference or activity which discloses several species of a claimed genus can be overcome directly under 37 CFR 1.131 only by a showing that the applicant completed, prior to the date of the reference or activity, all of the species shown in the reference. *In re Stempel*, 241 F.2d 755, 113 USPQ 77 (CCPA 1957).
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> It is not necessary for the affidavit evidence to show that the applicant viewed his or her invention as encompassing more than the species actually made. **The test is whether the facts set out in the affidavit are such as would persuade one skilled in the art that the applicant possessed so much of the invention as is shown in the reference or activity**. *In re Schaub*, 537 F.2d 509, 190 USPQ 324 (CCPA 1976). (Emphasis added.)

The Combined Declaration under 37 C.F.R. § 1.131 and § 1.132 submitted by Applicants

[1] By submitting the § 131 Declaration, Applicants did not concede that the subject matter of present claims 45-46, 58-61, and 72 was obvious over the combination of Relyveld and Poser.

(and resubmitted herewith) states that at least as much of the subject matter disclosed by Poser was reduced to practice by Applicants prior to July 31, 1998 (the earliest priority date of Poser). As evidence, Applicants provide a copy of PCT/US97/18528 (Exhibit A), which was filed on October 16, 1997, and which teaches the preparation of a vaccine delivery composition that includes a calcium phosphate and an antigen (see, e.g., page 8, lines 2-5, and page 35, line 11, through page 36, line 4, of PCT/US97/18528; a copy of which is enclosed). The Declaration also attests that D. Duke Lee and Maria Aiolova, who are named as the inventors of the present application and as co-inventors on PCT/US97/18528, are the only inventors of the relevant subject matter described in PCT/US97/18528; the third inventor named on PCT/US97/18528, Christian Rey, did not contribute to that subject matter.[2] Because the attached Declaration under 37 C.F.R. § 1.131 clearly shows Applicants' possession of "so much of the claimed invention" as Poser discloses, Poser can now be withdrawn as prior art to the present application (see M.P.E.P. § 715.03(I)(B), *supra*).

In the absence of Poser, the rejection of claims 45-54 and 56-72 for obviousness in view of Relyveld alone cannot be sustained. Relyveld discloses an aqueous gel of calcium phosphate for preparing adsorbed vaccines (see, e.g., the abstract); Relyveld fails to teach or suggest a calcium phosphate-based vaccine formulation having a solids content of greater than or equal to 40 wt%. Moreover, by disclosing an aqueous gel formulation, Relyveld directly teaches away from the composition recited in present claims 45-54 and 56-72, which further rebuts the conclusion that Relyveld, in combination with any reference, would lead the skilled artisan to

[2] Applicants regretfully note that Inventor D. Duke Lee is deceased. Accordingly the Declaration is only signed by the co-inventor, Maria Aiolova; a copy of his Certificate of Death is enclosed.

Applicants' claimed immunological vaccine delivery composition (see, e.g., M.P.E.P. § 2144.05(III); "A *prima facie* case of obviousness may also be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997)"). Accordingly, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 45-54 and 56-72 over Relyveld in combination with Poser be withdrawn.

Relyveld in Combination with Poser and Classen

Claims 49-54, 56-57, and 64-72 are rejected under 35 U.S.C. § 103(a) for obviousness over Relyveld in combination with Poser and Classen. For the reasons further elaborated above, Poser is not prior art to the present application. As was previously asserted in the prior Reply to Final Office Action, filed on February 15, 2006, in the absence of Poser, this rejection also cannot be sustained. Neither Relyveld nor Classen, either singly or in combination, teach or suggest each and every limitation of present claims 49-54 56-57, and 64-71. Relyveld is discussed *supra*. Classen discloses a traditional vaccine formulation that contains, *inter alia*, an immunogen (see, e.g., col. 15, line 30, through col. 20, line 34) and an adjuvant (e.g., calcium phosphate salts; col. 20, lines 35-50), which are diluted in phosphate buffered saline (PBS; see, e.g., col. 35, lines 23-38). Classen, like Relyveld, fails to teach or suggest the administration of an immunogen using a composition having a solids content of greater than or equal to 40 wt% and that is hardenable. The Examiner does not argue that this rejection has merit absent Poser, and Applicants believe that it does not. Thus, Applicants respectfully request that the 35 U.S.C. § 103(a) rejection of claims 49-54, 56-57, and 64-72 over Relyveld in combination with Poser

and Classen be withdrawn.

Relyveld in Combination with Gerhart and Constantz

Claims 45-46, 58-61, and 72 are rejected under 35 U.S.C. § 103(a) for obviousness over the combination of Relyveld, Gerhart, and Constantz. The Examiner states that it would be obvious to combine Relyveld, which "teaches the state of art for using calcium phosphate to improve the efficacy of vaccine formulations," with Gerhart and Constantz, which disclose hardenable calcium phosphate compositions that are nanocrystalline and suitable for use as drug delivery vehicles, to produce the immunological vaccine delivery composition recited in present claims 45-46, 58-61, and 72. The Examiner concludes:

> it would have been obvious to one of ordinary skill in the art at the time of invention to modify [the] physical characteristics of Relyveld's composition into an injectable paste, as suggested by Gerhart and Constantz, and formulate a hardenable calcium phosphate formulation that is easily administered to a site of interest, because the ordinary artisan would have had a reasonable expectation of success in achieving the same clinical result. (Office Action, pp. 7-8.)

Applicants respectfully traverse this rejection.

The Legal Standard for Obviousness under 35 U.S.C. § 103

To establish a *prima facie* case of obviousness under § 103, the Examiner must demonstrate that the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art. See 35 U.S.C. § 103(a) (Supp. III 1997); *In re Dembiczak*, 175 F.3d 994, 998, 50 USPQ2d 1614, 1616 (Fed. Cir. 1999). Whether or not a claimed invention is obvious is a legal conclusion based on underlying factual inquiries,

including: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) objective evidence of nonobviousness. *Id.*

Importantly, where "claimed subject matter has been rejected as obvious in view of a combination of references, a proper analysis under § 103 requires, *inter alia*, consideration of two factors: (1) whether the prior art would have suggested to those of ordinary skill in the art that they should . . . carry out the claimed process; and (2) whether the prior art would have revealed that in so . . . carrying out, those of ordinary skill would have a reasonable expectation of success." *In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438, 1442 (Fed. Cir. 1991). Furthermore, "[b]oth the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chem. Co.*, 837 F.2d 469, 473, 5 USPQ2d 1529, 1531 (Fed. Cir. 1988). As the Federal Circuit recently observed:

> A critical step in analyzing the patentability of claims pursuant to section 103(a) is casting the mind back to the time of invention, to consider the thinking of one of ordinary skill in the art, guided only by the prior art references and the then-accepted wisdom in the field. . . . Most if not all inventions arise from a combination of old elements. . . . Thus, every element of a claimed invention may often be found in the prior art. . . . However, identification in the prior art of each individual part claimed is insufficient to defeat patentability of the whole claimed invention. . . . Rather, to establish obviousness based on a combination of the elements disclosed in the prior art, *there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant.*

In re Kotzab, 217 F.3d 1365, 1369-70, 55 USPQ2d 1313, 1316 (Fed. Cir. 2000)(emphasis added)(citations omitted). The evidence of a suggestion, teaching, or motivation to combine "must be clear and particular." *Dembiczak*, 175 F.3d at 999. "Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness."

Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH, 139 F.3d 877, 880, 45 USPQ2d 1977, 1981 (Fed. Cir. 1998). "Broad conclusory statements regarding the teaching of multiple references, standing alone, are not 'evidence.'" *Id.*

Thus, the case law clearly mandates that, even if the Examiner identifies every element of a claimed invention in various pieces of the prior art, this alone is insufficient to negate patentability. Otherwise, "rejecting patents solely by finding prior art corollaries for the claimed elements would permit an examiner to use the claimed invention as a blueprint for piecing together elements in the prior art to defeat the patentability of the claimed invention." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457 (Fed. Cir. 1998). To avoid hindsight based on the invention to defeat patentability of the invention, the Federal Circuit requires an Examiner to show a motivation to combine the references that create the case of obviousness. *Id.* That is, "the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed." *Id*; emphasis added.

Claims 45-46, 58-61, and 72 are Not Obvious Over the Combination of Relyveld, Gerhart, and Constantz

In the present case, the Examiner has merely identified each element of the present claims in the cited art, but has failed to demonstrate that the cited references teach, suggest, or motivate the skilled artisan to combine their reference teachings to yield the invention of claims 45-46, 58-61, and 72.

As is discussed above and as has been discussed previously, Relyveld discloses an aqueous gel of calcium phosphate for preparing adsorbed vaccines; the aqueous gel has a solids content two orders of magnitude less than the vaccine delivery composition of present independent claims 45, 59, and 60, and claims dependent therefrom (see, e.g., the Abstract, and Applicants' prior Reply to Examiner's Final Action, dated January 15, 2004). Relyveld fails to teach or suggest substantially increasing the solids content of the aqueous gel composition beyond that of about 3.3 wt %, and certainly not greater than or equal to 40 wt%, as is recited in present claims 45-46, 58-61, and 72. Moreover, by disclosing an aqueous gel formulation, Relyveld directly teaches away from a vaccine delivery composition having a high solids content, such as the vaccine delivery composition of present claims 45-46, 58-61, and 72. This clearly contrasts with the Examiner's conclusion that the skilled artisan would find motivation in Relyveld to combine it with references that disclose hardenable calcium phosphate pastes so as to arrive at Applicants' claimed immunological vaccine delivery composition (see, e.g., M.P.E.P. § 2144.05(III), *supra*).

The Examiner acknowledges that Relyveld "lacks in teachings a paste formulation having about 40% solids content" (Office Action, p. 4). Applicants wish to clarify that the deficiencies of Relyveld are greater than this. Relyveld merely discloses the use of dilute aqueous vaccine adsorbing gels. Relyveld does not disclose vaccine adsorbing pastes, nor does it provide any suggestion to increase the solids content of the gels beyond about 3.3 wt % so as to achieve a paste-like consistency. The absence in Relyveld of any teaching or suggestion to reformulate the dilute aqueous gel as a paste or to significantly increase the solids content of the dilute gel formulation creates an insufficient basis from which to conclude that Relyveld provides any

motivation to combine its disclosure with that of a reference that discloses paste formulations.

To remedy the deficiencies of Relyveld, the Examiner cites Gerhart and Constantz. These references are not directed to the preparation of vaccine compositions, nor do they teach or suggest that calcium phosphate containing gel formulations should be reformulated as pastes. Instead, Gerhart is directed to a "biodegradable cement composition adapted for use in the surgical repair of living bone and for the controlled release of pharmaceutical agents" (Gerhart, col. 4, lines 19-22), while Constantz discloses

> calcium phosphate cements [that] may be used for a variety of purposes, such as any form of connective tissue replacement, including bone cement, an injected prosthetic implant, a prosthetic orthopaedic or dental implant, as a root canal filler, a prophylactic injection to augment weak osteoporotic bone, to fill voids resulting from fracture reduction, or a vehicle for drug delivery. (Constantz, col. 6, lines 56-62.)

Both Gerhart and Constantz disclose that their cement compositions can be used as drug delivery vehicles, but neither discloses that the cement compositions can or should be used as immunological vaccine delivery compositions. Thus, Gerhart and Constantz fail to provide any teaching, suggestion, or motivation to combine their reference teachings with Relyveld to yield the invention of claims 45-46, 58-61, and 72. The mere fact that the references can be combined or modified does not render the resultant combination obvious unless the prior art references also suggest the desirability of the combination, which, in this case, they do not (*In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990)). Because there is no motivation in Relyveld to combine its teachings with that of Gerhard and Constantz, and vice versa, the Examiner has not met his burden of establishing a *prima facie* case of obviousness. Accordingly, the rejection of claims 45-46, 58-61, and 72 should be withdrawn.

The Suggestion to Combine the Cited References and the Expectation of Success is Found Solely in Appellants' Disclosure

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the prior art must suggest the claimed combination and provide a reasonable expectation of success; these elements cannot be found solely in Applicants' disclosure (see *In re Vaeck*, *supra*, and *In re Dow Chem. Co.*, *supra*). As is discussed above, Relyveld fails to teach or suggest modifying the dilute aqueous gel vaccine formulation to provide a paste formulation, and Gerhart and Constantz fail to provide any teaching, suggestion, or motivation to combine their calcium phosphate cement compositions with the dilute aqueous gel vaccine formulation of Relyveld to yield the composition recited in claims 45-46, 58-61, and 72. The Examiner has not established a clear motivation provided solely from the cited references that would guide the skilled artisan to combine the reference teachings to yield the invention recited in claims 45-46, 58-61, and 72 prior to the disclosure of Applicants' present invention, nor any expectation of success other than that derived from the teachings of Applicants' disclosure. Therefore, both the motivation to combine the cited references and the reasonable expectation of success must be derived solely from the teachings of Applicants' disclosure.

Use of Applicants' disclosure to provide a motivation for combining the cited references and to derive a reasonable expectation of success is an improper use of hindsight and cannot form the basis for an obviousness rejection. The Federal Circuit has repeatedly cautioned against the "insidious effects of hindsight" in making obviousness determinations. *Life Technologies, Inc. v. Clontech Labs, Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000). More specifically, the court has stated:

> it is impermissible to first ascertain factually what [Applicants] did and then view the prior art in such a manner as to select from the random facts of art only those which may be modified and then utilized to reconstruct appellants invention from such prior art. (*Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 227 U.S.P.Q. 543 (Fed. Cir. 1985).)

To avoid the use of hindsight, the M.P.E.P. has adopted the same view, stating that "the mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness," and that the art must provide "an objective reason to combine the teachings." M.P.E.P. § 2143.01, *supra*. Further, a generally high level of skill in the art cannot be relied upon to provide such a reason. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308 (Fed. Cir. 1999). Thus, absent a specific motivation to combine references, a *prima facie* case of obviousness cannot be made.

Because the prior art does not teach, suggest, or motivate the skilled artisan to prepare the composition of claims 45-46, 58-61, and 72, and because the cited references fail to provide a reasonable expectation of success for making or using such a composition, absent the guidance provided by Applicants' disclosure, Applicants respectfully submit that the Examiner has relied upon improper hindsight to form the basis for the rejection of claims 45-46, 58-61, and 72 for obviousness. Therefore, Applicants respectfully request that, for this reason as well, the rejection of claims 45-46, 58-61, and 72 under 35 U.S.C. § 103(a) over the combination of Relyveld, Gerhart, and Constantz should be withdrawn.

CONCLUSION

In view of the above remarks, Applicants respectfully submit that the claims are in condition for allowance, and such action is respectfully requested.

Enclosed is a Petition to extend the period for replying for three months, to and including November 6, 2006, as November 4, 2006, fell on a Saturday, and a check in payment of the required extension fee.

If there are any other charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

Date: Nov. 6, 2006

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